PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES
(MBHB Case No. **02-312-G (600.041)**)

In re the Application of: Vargeese et al.	
Serial No: 10/780,447	**Group Art Unit:** 1623
Filed: April 30, 2003	**Examiner:** Eric Olsen
For: Conjugates and Compositions for Cellular Delivery	**Confirmation No.:** 2130

BRIEF ON APPEAL

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BRIEF ON APPEAL

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This is an appeal from the Final Rejection of the Primary Examiner dated July 13, 2007 and Advisory Action dated September 27, 2007. This brief is submitted along with the large entity fee of five hundred ten dollars ($510). A notice of appeal was filed on January 16, 2008. In the event of any variance between the amounts enclosed and the Patent and Trademark Office charges, the Commissioner is authorized to charge or credit any difference to our Deposit Account No. 13-2490.

Contents

Real Party in Interest

The above-mentioned application is assigned to Sirna Therapeutics, Inc., which is a wholly owned subsidiary of Merck & Co., Inc. An assignment from the inventors of the application to Sirna Therapeutics, Inc. was recorded at Reel 015589, Frame 0591 on July 19, 2004.

Related Appeals and Interferences

This application is a continuation-in-part of co-pending U.S. Patent Application Serial No. 10/427,160, filed April 30, 2003 which is also currently on appeal.

Status of Claims

Claims 1-4, 7-14 and 17-19 were previously canceled. Claims 5-6, 15-16 and 20-21 are pending in this application and stand rejected. Claims 5-6, 15-16 and 20-21 are appealed herein. A copy of the claims on appeal is attached in Appendix A.

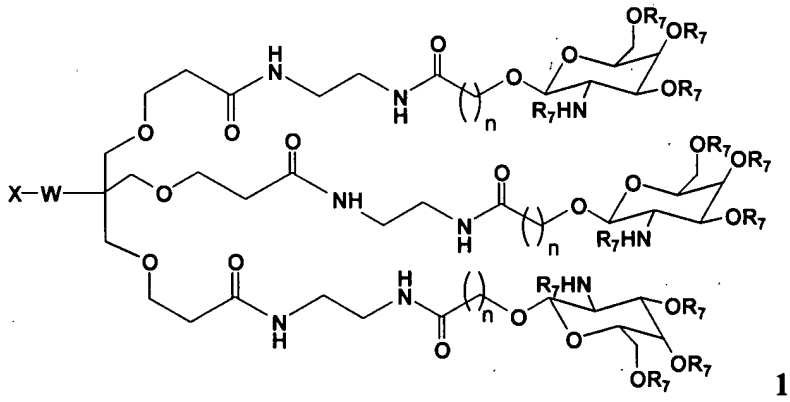
Status of Amendments

A Response to Final Office Action mailed July 13, 2007 was filed on September 13, 2007 presenting arguments to the standing obviousness rejection. In an Advisory Action mailed September 27, 2007, the Examiner considered the arguments provided in the Response to Final, but maintained the obviousness rejection nonetheless.

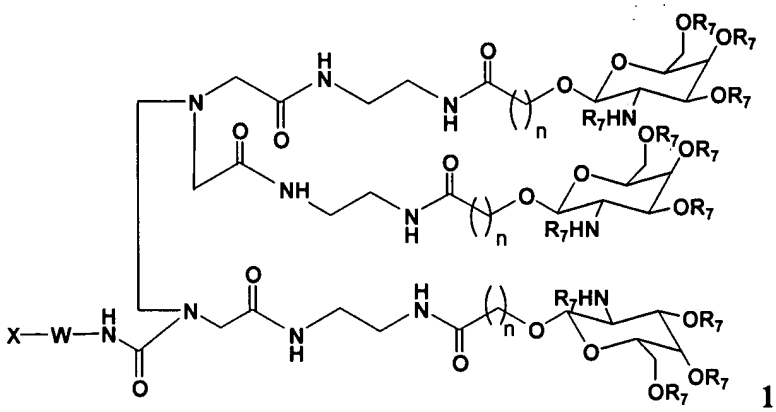
Summary of the Claimed Subject Matter

The instant invention is drawn to conjugates that facilitate delivery of molecules into a biological system, such as, for example, living cells. Therapeutic bioavailability, pharmacodynamic, and pharmacokinetic parameters can be modulated through the use of such conjugates.

Specifically, the present invention is directed to compounds of the formulae 119 and 121 depicted below, wherein each X comprises a short interfering RNA (siRNA) molecule, each W comprises a linker molecule or chemical linkage that can be present or absent, each R_7 independently comprises an acyl group that can be present or absent, and each n is independently an integer from about 1 to about 20 (see Specification at page 55, line 18 to page 56, line 8; and at page 57, line 11 to page 58, line 6).



119



121

In an embodiment of the invention, the compounds of formulae 119 and 121 contain the linker W comprising an amide, a phosphate, a phosphate ester, a phosphoramidate, or a thiophosphate ester linkage. Compounds depicted in Figures 46-48 are representative examples. In another embodiment, X comprises a siRNA molecule comprising a sense strand and an antisense strand, wherein the sense strand is conjugated with a compound of formula 119 or 121.

Grounds of Rejection to be Reviewed on Appeal

The only issue on appeal is whether the subject matter of claims 5-6, 15-16 and 20-21 is obvious under 35 U.S.C. § 103(a) over Low *et al.* (PCT publication WO 90/12096) in view of Connolly *et al.* (*Journal of Biological Chemistry*, 257 (2), 939-945 (1982)).

Argument

Claims 5-6, 15-16 and 20-21 are not obvious over Low in view of Connolly and Li

Applicants respectfully submit that the instant claims are not *prima facie* obvious over Low in view of Connolly and Li because the references, either alone or in combination, do not teach the claimed compounds.

The prior art references, either alone or in combination, simply do not teach the specific tri-galactosamine conjugates of formulae 119 or 121. The conjugates of formula 119 require an alkyl-carboxy-amino-ethyl-amino-carboxy-ethyloxy group between the methylene spacer and galactosyl group in each of the three arms of the tri-galactosamine compound. In addition, a short interfering RNA (siRNA) is attached to one end of a linker portion of each of the conjugates. The other end of the linker is attached to the three arms *via* a methylene spacer. Similarly, the conjugates of formula 121 require an alkyl-carboxy-amino-ethyl-amino-carboxy-methylamino group, representing one arm, and a di(alkyl-carboxy-amino-ethyl-amino-carboxy-methyl)-amino group, each representing one of the other two arms. Again, conjugates of formula 121 also require an siRNA attached to one end of a linker, with the other end of the linker being attached to the two arms *via* an amide-methylene spacer.

By contrast, Connolly teaches tri-galactosamine compounds wherein the galactosyl portion is bonded directly to a methylene spacer in each of the three arms. Low teaches enhancing transmembrane transport of biologically active compounds. In addition, Li describes a dsRNA molecule, which acts to specifically inhibit expression of a target gene.

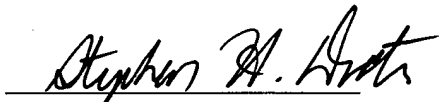
The Examiner contends that "[i]t would have been obvious to one of ordinary skill in the art at the time of the invention to modify the compounds of Low et al. in view of Connolly et al. by attaching the dsRNA molecules of Li et al. by the sense strand, as the exogenous molecule described

by Low et al," to arrive at the instant compounds (see Final Office Action, at page 6, lines 7-10). Applicants respectfully disagree, since the teachings of Low, Li or Connolly, either alone or in combination, do not teach the compounds of the instant invention, *i.e.* tri-galactosyl compounds with either an alkyl-carboxy-amino-ethyl-amino-carboxy-ethyloxy or an alkyl-carboxy-amino-ethyl-amino-carboxy-methylamino substituent in each arm and an siRNA molecule attached to one end of a linker. It would not have been obvious to substitute the methylene spacer in each arm of the tri-galactosides as taught in Connolly with the alkyl-carboxy-amino-ethyl-amino-carboxy-ethyloxy or alkyl-carboxy-amino-ethyl-amino-carboxy-methylamino groups of the claimed compounds, since the latter groups are structurally distinct from a methylene group.

In other words, the compounds disclosed in Connolly are not compounds "of similar structure to the claimed compounds" (see Final Office Action, at page 6, lines 14-18). The Examiner would have Applicants believe that any and all compounds having a tri-galactosyl backbone would be obvious in view of Connolly. In fact, both the alkyl-carboxy-amino-ethyl-amino-carboxy-ethyloxy and the alkyl-carboxy-amino-ethyl-amino-carboxy-methylamino groups have a distinct and separate status in the art and are thus expected by those skilled in the art to have different chemical and biological properties from compounds that have a mere methylene spacer. Applicants have discovered, through much experimentation, that the compounds of formulae 119 and 121are useful conjugates to facilitate delivery of molecules into a biological system.

For these reasons, the cited references do not render the claims obvious. As such, Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,

Date: By: 

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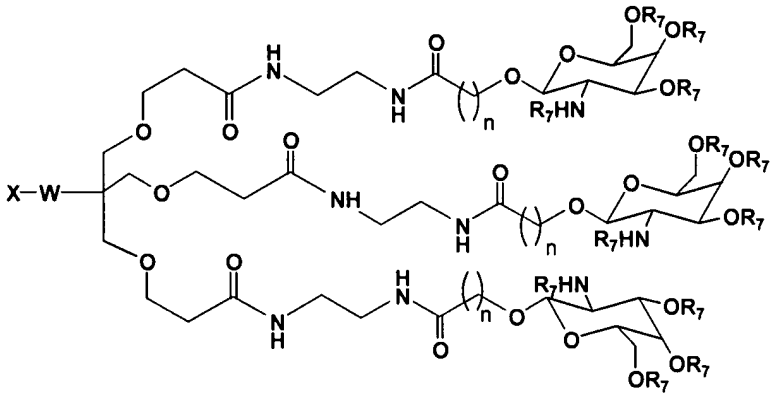
312-913-0001

Appendix A

1-4. (Canceled).

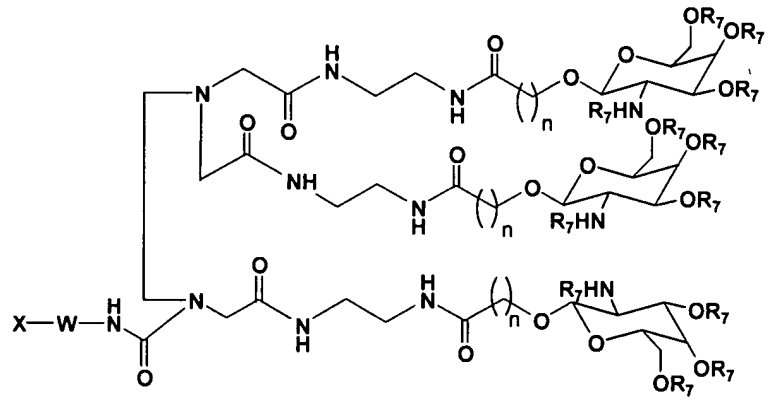
5. (Previously Presented) A compound having Formula 119:



119

wherein X comprises a short interfering RNA (siRNA) molecule; W comprises a linker molecule or chemical linkage that can be present or absent, each R7 independently comprises an acyl group that can be present or absent, and each n is independently an integer from about 1 to about 20.

6. (Previously Presented) A compound having Formula 121:



121

wherein X comprises a short interfering RNA (siRNA) molecule; W comprises a linker molecule or chemical linkage that can be present or absent, each R7 independently comprises an acyl group that can be present or absent, and each n is independently an integer from about 1 to about 20.

7-14. (Canceled).

15. (Original) The compound of claim 5, wherein W comprises a linker molecule or chemical linkage selected from the group consisting of amide, phosphate, phosphate ester, phosphoramidate, or thiophosphate ester linkage.

16. (Original) The compound of claim 6, wherein W comprises a linker molecule or chemical linkage selected from the group consisting of amide, phosphate, phosphate ester, phosphoramidate, or thiophosphate ester linkage.

17-19. (Canceled).

20. (Previously Presented) The compound of claim 10, wherein said siNA molecule comprises a sense strand and an antisense strand, and wherein said sense strand is conjugated with a compound comprising Formula 119.

21. (Previously Presented) The compound of claim 11, wherein said siNA molecule comprises a sense strand and an antisense strand, and wherein said sense strand is conjugated with a compound comprising Formula 121.